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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,337	WINDISCH ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08-28-2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20, 22-43* is/are pending in the application.

4a) Of the above claim(s) *9,18 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-17,19,20,22-28 and 30-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of the claims. Claims 1-20, 22-43 are pending. Claims 1, 6-10, 15-18, 20 and 26-29 have been amended, claim 21 has been canceled and claims 42 and 43 have been added by Applicants' amendment filed on 08-28-2008. Claims 9, 18, and 29 were previously withdrawn from further consideration pursuant to 37 CFR1.14(b) as being drawn to nonelected species. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
3. Therefore, claims 1-8, 10-17, 19, 20, 22-28 and 30-43 are currently under examination to which the following grounds of rejection are applicable

Response to arguments

Rejections/Objections withdrawn in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 112

In view of Applicants' amendment of claim 20 to recite the step "isolating the polypeptide of interest form the host cell", rejection of claim 20 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps, has been withdrawn.

Rejections maintained in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 103

Claims 1-3, 6-8, 10-12, 15-17, 19, 21-23, 26-28, 30-41 remain rejected, and claims 42 and 43 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Peleg et al., (WO 03/004599 A2, Date of Publication 16-Jan-2003) in view or Matsuda et al. (J. of Bacteriology, 1985, p. 1222-1228) or Ishii et al., (Journal of Fermentation and Bioengineering , 1994, pp. 591-597) or Kim et al., (Biotechnology Letters, 2001, pp. 1067-1071).

Reply to applicant arguments as they relate to rejection of claims 1-3, 6-8, 10-12, 15-17, 19, 21-23, 26-28, 30-41 under 35 USC § 103

At pages 11 and 12 of Remarks, Applicants assert that there is not suggestion or motivation to combine the teachings of Peleg et al., with Matsuda et al. Ishii et al., or Kim et al.,. Specifically, Applicants content that "The primary reference, Peleg does not teach, disclose, or suggest an expression vector that comprises a polynucleotide sequence that codes for a fusion protein which includes the claimed signal sequence of the gac gene of *P. dimimuta*. Peleg deals with making a fusion polypeptide by introducing an expression construct containing a viral-derived peptide". In addition Applicants allege that "The references sought to be intermeshed with Peleg appear to be concerned with various disparate genetic and molecular biological characterizations of the gac gene in some species of Pseudomonas, and of the expression of gac protein in *E. coli*, but nothing in the combination or in any single reference reveals any motivation or suggestion that would have led a person of ordinal skill to modify Peleg to make an expression vector as called for in the claims". [emphasis added]. Such is not persuasive.

As stated in the office action filed on 12-12-2007, Peleg clearly discloses "that transport of proteins through the inner membrane to the periplasmic space requires the inclusion of a signal peptide" (p. 3, lines 8-10). Indeed, Peleg exemplifies construction of vectors comprising a polylinker sequence being operably linked to the signal sequence and a prokaryotic promoter being operably linked to the periplasmic targeting sequence of a virally derived TAT (p. 11, lines 12-18; p. 20, line 14-17). Moreover, incorporation of a bacterial signal sequence in frame with the TAT-derived peptide and the protein of interest provides for cleavage of the signal sequence and the TAT-derived sequence, providing a mature, properly folded readily isolatable and purifiable protein (p. 7, lines 12-15). Note that the inclusion of TAT –mediated transport to a signal sequence for expression of the heterologous proteins in a prokaryotic system enhances proper folding of the conjugated protein (p. 6, lines 28-30). Furthermore, Peleg et al., discloses the structure and functionality of bacterial signal peptides for transport of proteins from the cytoplasm to the periplasmic space. Peleg describes that "during the transport of the proteins out of the cytoplasm, the signal peptide is typically removed by signal peptidase thereby leaving a mature protein at the desired non-cytoplasmic location" (p. 27, lines 1-5). Furthermore, Peleg discloses different cleavage recognition sequences from mycoplasmas, other gram positive bacteria and *E. coli* well that were well known in the art (p. 26, lines 27-30 bridging to p. 27, lines 1-19). The combined disclosure of Matsuda, Kim and Ishii teaches a signal sequence of the gac gene of *Pseudomonas diminuta*. Note that the nucleotide sequence GL 7-ACA acylase gene taught by Matsuda et al. comprises SEQ ID No. 2 , i.e., signal peptide, and SEQ ID NO. 5, i.e., promoter region and ribosomal biding site as set forth and claimed in the instant invention. Accordingly, a person of ordinary skill would have recognized the signal sequence of the gac

gene of *P. diminuta* is one of a finite number of signal sequences available in the art known to be useful for the released of a polypeptide of interest into the periplasm of a host cell, as Matsuda taught that the signal peptide of glutaryl (GL) 7-ACA acylase gene from *Pseudomonas sp.* GK16 was useful for translocation of the GL 7-ACA acylase into the periplasm in *E. coli*. The signal sequence of the gac gene of Pseudomona should reasonably be expected to release the fusion protein of interest into the periplasm of the host cell in the fusion protein taught by Peleg for the same reason it secretes the mature, active acylase into the periplasm in *E. coli* as disclosed by the combined references of Matsuda et al. Ishii et al., or Kim. Thus it would *have been obvious* to a person of ordinary skill in the art to try the he signal sequence of the gac gene of *Pseudomonas diminuta* in an attempt to provide an improved formulation of the expression vector of Peleg encoding a fusion protein comprising a protein of interest and a signal sequence, as a person with ordinary skill has a good reason to pursue known options within his technical grasp.

At page 12 of Remarks, Applicants contend that though "It is well accepted in the art, that while many genetic recombinations "might" be useful, the science is generally not predictable. There would have been no reasonable expectation for success in substituting the gac signal sequence as claimed by Applicants into an expression vector according to the process of Peleg, absent some indication or direction from the references that such a substitution should be done or would work. But there is none. Ishii teaches that "the signal sequence is foreign to *E. coli* and not effectively recognized by *E. coli* signal peptidase" (page 596, last paragraph). Accordingly, the combined disclosure of Ishii and Peleg would actually have served to

discourage a person of ordinary skill in the art who read these references from attempting to make the proposed combination, and would, if any thing, have lead one away from Applicants invention [emphasis added]. Such is not persuasive.

Ishii clearly discloses high-level production of 7ACA in *E. coli*. Indeed, because of the low productivity of the active 7ACA in the original host strain, e.g., *Pseudomonas diminuta*, *E. coli* is selected as the host for secretion of the mature protein from the precursor, said precursor comprising the *P. diminuta* signal peptide, wherein the enzymatically active acylase isolated from *E. coli* was found in the periplasm (p. 595, col. 1, paragraph 1; p. 595, col. 2, paragraph 1). At page 596, col. 1, last paragraph, referred by Applicants, Ishii discloses reduced expression of active acylase from 5-to 2-fold which is speculated to be related to the signal sequence of *P. diminuta* as this signal is foreign in *E. coli*. Note that expression of acylase in the specific example cited by Applicants is under the control of a *E. coli* tryptophan promoter and not a *P. diminuta* promoter as claimed by the instant invention. Therefore, there is not real evidence to conclude that the signal peptide of *P. diminuta* would have not worked in the construct of Peleg for expression of the heterologous protein in *E. coli*, much less that the reduce expression of the plasmid in the example cited by Applicants would preclude the skilled artisan from having a reasonable expectation of success, as evidenced by the generation of said expression vector for release of the polypeptide of interest into the periplasm of *E. coli* in the instant specification by following the combined teachings of Peleg et al., Matsuda et al. Ishii et al., and Kim et al.,.

Claims 4, 5, 13, 14, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peleg et al., (WO 03/004599 A2, Date of Publication 16-Jan-2003) in view of Matsuda et al.

(J. of Bacteriology, 1985, p. 1222-1228), Ishii et al., (Journal of Fermentation and Bioengineering , 1994, pp. 591-597), Kim et al., (Biotechnology Letters, 2001, pp. 1067-1071) as applied to claims 1-8, 10-17, 19-28, 30-43 above, and further in view of Kwon et al., WO 01/057217, (Date of publication 9 August 2001).

At page 13 of Remarks, Applicants allege "even if there was some motivation to combine these teachings to make an "obvious" combination, and there is not, there still is no teaching, suggestion, or disclosure within Kwon to lead one of skill in the art to make the presently imagined combination. Kwon is directed toward the expression, in *E. coli*, of a heterologous fusion protein comprising a polypeptide of interest and an *E. coli* heat stable enterotoxin I1 signal sequence. No indication is given in Kwon that any signal sequence not native to *E. coli* (such as the P. diminuta-derived signal sequence of the present claims) would be of any use in an expression system for producing a polypeptide of interest according to Applicants" claims. The mere fact that Kwon discloses hIFNαt-2a and hIFNα-2b as a polypeptide of interest in one expression system says nothing about the performance of those proteins in other expression systems, or makes any suggestion as to what, if any, alternative expression system might be suitable". Such is not persuasive.

Kwon et al., complements the teachings of Peleg et al., Matsuda et al. Ishii et al., and Kim et al.,. by disclosing expression vectors encoding fusion proteins which carry a signal peptide attached to their N-terminal for the secretive production of hIFNα subtypes 2a and 2b (p. 1, lines 6-13; p. 2, lines 27-28; p.3, lines 23-27). Moreover, Kwon et al., successfully exemplified secretion of interferon alpha 2A or 2B in *E. coli* transformants into the periplasm at high productivity (p. 8, lines 1-2). Regardless of the productivity of the system, transport of

proteins through the inner membrane to the periplasmic space requires the inclusion of a signal peptide into the fusion protein, so any construct comprising a signal peptide would reasonably be expected to release a mature protein into the periplasm of the host cell, absent evidence to the contrary. Thus the interferon alpha 2 of Kwon would had been released into the periplasmic space when expressed in the vector of Peleg et al., Matsuda et al. Ishii et al., and Kim et al., for the same reason it is released from the fusion protein encoded by the vector of Kwon.

New Grounds of rejection

Objection

Claim 10 is grammatically incorrect in its recitation of "a polynucleotide which encodes a fusion protein containing which including the signal sequence of the gac gene of *Pseudomonas diminuta* and of a polypeptide of interest". Appropriate correction is requested.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 16, 27, 42 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claims 16 and 27 have been amended to recite "said vector further comprises a second polynucleotide … wherein the second polynucleotide is operatively linked to the polynucleotide encoding the fusion protein". It is unclear whether the second polynucleotide operatively linked

to the polynucleotide encoding the fusion protein is expressed from the promoter of the polynucleotide encoding the fusion protein, from its own promoter or the first and second polynucleotides are operationally linked in a different way. Thus, claims 16 and 27 embrace several embodiments and hence, it is unclear what its metes and bounds are. It would be remedial to amend the claim language to clearly delineate between the different possibilities.

New claims 42 and 43, subpart b) recite "second polynucleotide comprising the promoter region and the ribosomal binding site of the gac gene of Pseudomonas diminuta, wherein the second polynucleotide is operatively linked to the first polynucleotide encoding the fusion protein comprising the signal sequence and the polypeptide of interest". It is unclear whether the second polynucleotide operatively linked to the polynucleotide encoding the fusion protein is expressed from the promoter of a) a first polynucleotide encoding the fusion protein, b) from its own promoter or both a) and b) are operationally linked in a different way. Thus, claims 42 and 43 embrace several embodiments and hence, it is unclear what its metes and bounds are. It would be remedial to amend the claim language to clearly delineate between the different possibilities.

Claim Rejections - 35 USC § 112- First paragraph- New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by amendment of the claims in the responses filed 08/28/2008. This is a New Matter rejection.**

New claim 43 recites "said vector comprising a) a first polynucleotide encoding a fusion protein which comprises i) the signal sequence, the promoter region and the ribosomal binding site of the gac gene of *Pseudomonas diminuta* and a polypeptide of interest". The response filed on 05-12-2008 does not indicate where support for the amendments regarding the promoter region and the ribosomal binding site of the gac gene of *Pseudomonas diminuta* in a first polynucleotide may be found. The specification as filed appears to provide sufficient disclosure for "a prokaryotic host cell transformed with an expression vector which is compatible with the host cell, said vector comprising a polynucleotide encoding a fusion protein comprising the signal sequence of the gac gene of Pseudomonas diminuta and a polypeptide of interest other than gac of *Pseudomonas diminuta*" (paragraph [0038]). Therefore, the specification does not appear to provide sufficient support for "the promoter region and the ribosomal binding site of the gac gene" in addition to the signal sequence of the gac gene of *Pseudomonas diminuta* and a polypeptide of interest". Though the specification appears to provide support for claim 43 subpart b) reciting "a second polynucleotide comprising the promoter region and the ribosomal binding site of the gac gene of *Pseudomonas diminuta"* in paragraph [0030] of the specification as filed stating, "an expression vector according to the present invention, wherein said vector further comprises a polynucleotide comprising the promoter region and the ribosomal binding site of the gac gene of Pseudomonas diminuta', it is unclear that Applicant was in possession of

the additional promoter and the ribosomal binding site of the gac gene of a first polynucleotide as required by claim 43, subpart i) .

Claim 43 will remain rejected until Applicant cancels all new matter.

Conclusion

Claims 1-8, 10-17, 19, 20, 22-28 and 30-43 are rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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